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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/713,545	11/15/2000	Russell N. Van Gelder	LBS-002COB	4526

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EXAMINER

LEFFERS JR, GERALD G

ART UNIT PAPER NUMBER

1636

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/713,545	<b>Applicant(s)</b> VAN GELDER ET AL.	
	<b>Examiner</b> Gerald G. Leffers Jr., PhD	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 42 and 44-54 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 42 and 44-54 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>7/16/2004</u> | 6) <input type="checkbox"/> Other: _____  |

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## **DETAILED ACTION**

### ***Response to Amendment***

Receipt is acknowledged of an amendment, filed on 1/5/2005, in which claim 43 was cancelled and in which claims 42 & 54 were amended. Claims 42 and 44-54 are pending and under consideration in the instant application.

Any rejection of record not addressed herein is withdrawn. In particular, applicants' arguments in the response filed on 1/5/2005 were persuasive with regard to the teachings of Kwoh et al and Gingeras et al and the lack of a demonstration of linear amplification as defined in the instant specification. The rejection made under 112 1<sup>st</sup> paragraph concerning the insertion of New Matter in the pending claims with regard to the use of multiple primers is maintained for reasons given below in response to applicants' arguments. The rejections for obviousness-type double patenting over previously issued claims are maintained for reasons of record. This action is Final.

### ***Information Disclosure Statement***

Receipt is acknowledged of an information disclosure statement (IDS) filed 7/16/2004. The signed and initialed PTO Form 1449 has been mailed along with this action. References cited previously in prosecution of the instant application have been lined-through in order to avoid duplicate printing on the face of any patent to issue from the instant application.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42, 44-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the Office Action mailed on 3/10/2004 and which are repeated below.**

Each of the rejected claims is directed to a multi-gene expression profile of a sample comprising a collection of linearly amplified specific nucleic acid messages, wherein said amplified specific nucleic acid messages each have an abundance which reflects the relative representation of specific nucleic acid messages within the sample. The rejected claims encompass embodiments where multiple primer/promoter sets are used to amplify the different target sequences within the sample.

The specification solely talks about generation of an expression profile for a sample where each amplified sequence is in an abundance that reflects the relative representation of a specific target sequence in the sample where a single primer linked to an RNA polymerase promoter is used to simultaneously amplify the different target sequences corresponding to the different genes in the profile. For example, the specification exemplifies an embodiment where an oligo-dT/T7 RNA polymerase promoter is used to direct linear amplification of multiple RNA species within a sample in a single reaction (e.g. Figure 1). Alternatively, the specification describes an embodiment featuring a T7 promoter primer comprising a sequence complementary

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to sequences found in messages for a family of G-coupled protein receptors to amplify a group of related, but different messages from a sample in a linear fashion (e.g. page 26, last paragraph).

Nowhere does the specification address the use of, for example, multiple and different primers to generate a gene expression profile of a sample where each amplified sequence is in an abundance that reflects the relative abundance of the target sequence in the original sample. Therefore, the broad scope encompassed by the instant claims is impermissible NEW MATTER. Applicants are invited to indicate those sections of the instant specification that would necessarily provide support for the use of multiple primer/promoter complexes in the methods of the rejected claims.

***Response to Arguments/112 1<sup>st</sup> Paragraph New Matter***

Applicant's arguments filed 1/5/2005 have been fully considered but they are not persuasive. The response essentially argues that the amendment of claims 42 and 53 now obviates the grounds of rejection presented above. It appears from reading applicants' response that a good faith effort was made to amend the claims to read on the use of a single primer operatively linked to an RNA polymerase promoter. However, as currently written, the claims can still be interpreted to use multiple primers to generate the multi-gene expression profile. The phrase "with a primer linked to an RNA polymerase promoter" still reads on embodiments where, for example, different primer sequences are linked to an RNA polymerase promoter and used in the same reaction to amplify multiple target RNAs. It would be remedial to amend the claim language to specify, "with a single primer linked to an RNA polymerase promoter".

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### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 42, 44-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,291,170 B1.

Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. **This rejection is maintained for reasons of record in the Office Action mailed on 3/10/2004 and which are repeated below.**

The claims of the '170 patent are directed to a multi-gene expression profile of a sample comprising a hybridizing target; and a hybridizing probe comprising a collection of amplified specific nucleic acid messages, which amplified specific nucleic acid messages have been amplified *in vitro* simultaneously with RNA polymerase and a single primer linked to a RNA polymerase promoter, wherein the amplified specific nucleic acid messages each have a relative abundance that qualitatively reflects the relative representation of specific nucleic acid messages within the sample. In these claims the collection of amplified specific nucleic acid messages is a probe hybridizing to the target to form a multi-gene expression profile. The amplified specific nucleic acid messages can be aRNA or cDNA. The gene expression profile can be obtain from a

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single cell, such as a neural cell. The gene expression profile can vary as a function of arousal state, behavior, drug treatment or development.

The instant claims differ from those of the '170 patent in that they do not explicitly state that the gene expression profile is generated by *simultaneous* amplification of the target sequence with a *single* primer/promoter complex. Therefore, the instant claims are broader genus claims that are anticipated by the claims of the '170 patent. Therefore, the claims of the '170 patent necessarily make obvious the instant claims.

Claims 42, 44-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,891,636. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. **This rejection is maintained for reasons of record in the Office Action mailed on 3/10/2004 and which are repeated below.**

The claims of the '636 patent are directed to a gene expression library derived from a cell or tissue sample comprising two or more specific nucleic acid messages of various abundances whose levels of representation to other messages within the population reflect the physiological state of the sample, thereby permitting diagnosis of a disease or conditions. The library is prepared by adding a primer complex to a population of messenger RNAs from a cell or cell population where the primer complex comprises a primer sequence complementary and hybridizable to a plurality of the population of mRNAs where the primer complex comprises a promoter sequence in antisense orientation. A double stranded complementary DNA (cDNA) is generated without using a secondary primer and the cDNA subsequently used to linearly

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transcribe multiple copies of antisense RNAs (aRNAs) that are quantified. Practicing the methods of the '636 patent would necessarily generate a gene expression profile where the relative abundance of the amplified sequences would reflect the relative representation of the different target sequences in the cell or cell populations. Two or more amplified sequences can be detected by hybridization techniques, such as northern or Southern hybridization. The sample can be derived from blood, brain, bone, heart and other cell types. The primer complex can consist essentially of poly(dT).

The instant claims differ from those of the '636 patent in that they do not explicitly state that the gene expression profile is generated by amplification of the target sequence with a primer/promoter complex that binds a plurality of target sequences and where the template cDNA is not generated with a second primer. Therefore, the instant claims are broader genus claims that are anticipated by the claims of the '636 patent. Therefore, the claims of the '636 patent necessarily make obvious the instant claims.

Claims 42, 44-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-6, 10 of U.S. Patent No. 5,545,522. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. **This rejection is maintained for reasons of record in the Office Action mailed on 3/10/2004 and which are repeated below.**

The claims of the '522 patent are directed to a process for amplifying at least one nucleic acid sequence using a single species of primer complex, the process consisting essentially of synthesizing a first nucleic acid by hybridizing the primer complex to the target sequence and



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extending the primer complex to form a first strand complementary to the target sequence and synthesizing a second strand complementary to the first strand, where synthesis of the second strand is primed by a 3' loop of the first strand, and subsequently transcribing copies of RNA initiated from the promoter region of the primer complex. The methods of the '522 patent can be practiced with a primer/promoter complex that binds the poly(A) tail of mRNA from eukaryotic cells. Synthesis of the first strand can occur in situ, within a single cell. The amplified RNA can be detected by hybridization to a labeled polynucleotide probe.

The instant claims differ from the cited claims of the '522 patent in that they do not explicitly state that the gene expression profile is generated by *simultaneous* amplification of the target sequence with a *single* primer/promoter complex. In embodiments encompassed by the claims of the '522 patent where multiple target sequences are amplified, a multi-gene expression profile would necessarily be generated where the amplified products would have necessarily been linearly amplified such that each amplified product would reflect the relative representation of the amplified target sequences in the original reaction sample. Therefore, with regard to the basic method of linear amplification of a plurality of target sequences in a sample, the instant claims are broader genus claims that are anticipated by the claims of the '522 patent. Therefore, the claims of the '522 patent necessarily make obvious the instant claims.

With regard to limitations regarding hybridization on a northern or Southern blot, and particular cell types, it would have been prima facie obvious to use techniques of hybridization and cell types well known in the art at the time of the invention.

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***Response to Arguments/Obviousness-Type Double Patenting***

Applicant's arguments filed 1/5/2005 have been fully considered but they are not persuasive. The response essentially argues that when any claim is found to be allowable, Terminal Disclaimers will be filed over the patents cited in making the rejections. The rejections remain in effect for the reasons outlined above.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G. Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 6:30-4:00.


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD  
Primary Examiner  
Art Unit 1636

ggl

  
**GERRY LEFFERS**  
**PRIMARY EXAMINER**